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EXAMINER	
BRISTOL, LYNN ANNE	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 07/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/666,122	LAUS ET AL.	
	Examiner	Art Unit	
	Lynn Bristol	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *21-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 12/10/04 6/14/06.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

1. Claims 1-30 are all the pending claims in this application.

Election/Restrictions

2. Applicant's election of Group I (Claims 1-20) with species for prostate cancer in the reply filed on June 5, 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-20 with species to prostate cancer are all the pending claims under examination, and claims 21-30 are withdrawn as being for non-elected subject matter.

Information Disclosure Statement

3. Except for U.S. patent reference #6 on the IDS of December 10, 2004, all of the U.S. patents, international patent applications and non-patent literature references cited in the IDSs of December 10, 2004 and June 14, 2006 have been considered and made of record. Reference 6 does not appear to have any relevancy to the specification so has not been considered or entered.

Applicants' IDS of January 12, 2004 appears to have been filed under the incorrect application no. The IDS does not list the same inventor or filing date of the instant application. Also, the U.S. patent references cited on the January 12, 2004 IDS do not appear to have any relevancy to the instant application. Accordingly, the

Examiner has not considered or entered the January 12, 2004 IDS. Applicants should consider withdrawing the January 12, 2004 IDS for filing in the proper application.

Inventorship/Oath/Declaration

4. The request to correct the inventorship of this nonprovisional application under 37 CFR 1.48(a) is deficient because Applicants' Response to Notice to File Missing Parts of April 26, 2004 does not appear to have included copies or originals of the following listed items:

a) Petition to Correct Inventorship;

b) Statement Under 37 C.F.R. §1.32(B)(2) by Inventor Small; and

c) Statement Under 37 C.F.R. §1.32(B)(2) by Inventor Rini.

Applicants' executed Oath/Declaration of April 26, 2004 lists only the five named inventors, having removed the names Brian Rini and Eric Small from the originally filed, unexecuted Oath/Declaration of September 19, 2003. Appropriate correction is required in order to enter the executed Oath/Declaration.

Applicants are also required to file an amended Application Data Sheet, which lists the named inventors for this application.

Sequence Listing

5. Applicant is required to provide the names of all inventors on the Sequence Listing pursuant to 37 CFR 1.823. The instantly filed Sequence Listing lists the names of Inventor Small and Inventor Rini. If Applicants intend to correct the inventorship as

discussed supra, they will need to provide a revised Sequence Listing, a computer readable form of the Sequence Listing and a statement. Please see the attached Notice to Comply Form, for which the Examiner has set a 3-month shortened statutory period for response. This is a provisional objection to the Sequence Listing Requirements based on Applicants providing the Office with documentation that inventorship is to be corrected.

Specification

6. The use of trademarks (e.g., PCR™, Isolex™) has been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

7. The abstract and specification are objected to for including the attorney docket no. of each of the pages. Each sheet of the specification shall contain no other information (see 37 CFR 1.171 (f)).

Claim Objections

8. Claims 5 and 6 are objected to because of the following informalities:

Claim 5 is drawn to non-elected subject matter for species of cancers;

Claims 5 and 6 are both drawn to prostate cancer and recite duplicate subject matter. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claim 2 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 is indefinite for reciting a "tumor-specific antigen" as it is unclear how the specific antigen differs from the "tumor associated antigen" and whether the specific antigen is from the same type of tumor as the intended population to be treated with the immunotherapeutic composition, or is an autologous antigen from the tumor of the same individual intended for treatment.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 13-15 and 17-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter, which was not described in the specification in such a way as to reasonably

convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a immunotherapeutic composition comprising an autologous APC from a prostate cancer patient stimulated *ex vivo* with a protein conjugate comprising an N- or C-terminal moiety having at least 70%, 80% or 90% sequence identity with the amino acid sequence of SEQ ID NO:1 (huPAP) or 3 (huGM-CSF).

The specification discloses a protein conjugate with a N- or C-terminal moiety comprising a TAA comprising human PAP of amino acid or encoded by DNA sequence, SEQ ID NOS: 1 or 2, respectively, and the APC binding protein comprising human GM-CSF of amino acid or encoded by DNA sequence, SEQ ID NOS: 3 and 4, respectively (Figure 7). The protein conjugate can also comprise a N- or C-terminal moiety having at least 70%, 80%, 90%, 95%, or 98% sequence identity with the sequence depicted in SEQ ID NO: 1 (huPAP) or an active fragment, derivative, or variant of huPAP (p. 5, lines 7-9) and a N- or C-terminal moiety having at least 70%, 80%, 90%, 95%, or 98% sequence identity with the sequence depicted in SEQ ID NO: 3 (huGM-CSF) or an active fragment, derivative, or variant of huGM-CSF (p. 5, lines 12-16). In example 1, and the only example of a protein conjugate, the DNA construct contains full length huPAP and huGM-CSF cDNAs. This same protein conjugate is used to stimulate autologous APCs from prostate cancer patients in Examples 3-6.

The specification does not provide sufficient written description as to the structural features of the claimed genus of huPAP and huGM-CSF nucleic acids and

encoded polypeptides and the correlation between the chemical structure and function of the genus of huPAP and huGM-CSF nucleic acids or amino acids, such as structural domains or motifs that are essential and distinguish members of the genus from those excluded. The specification does not disclose a single species with less than 100% sequence identity for either of the huPAP or huGM-CSF nucleic acids or encoded polypeptides comprising the protein conjugate.

A "representative number of species" means that the species, which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the genus. " See Enzo Biochem, 323 F.3d at 966, 63 USPQ2d at 1615; Noelle v. Lederman, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004)("[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated."). "A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when ... the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed." In re Curtis, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004)(Claims directed to PTFE dental floss with a friction-enhancing coating were not

supported by a disclosure of a microcrystalline wax coating where there was no evidence in the disclosure or anywhere else in the record showing applicant conveyed that any other coating was suitable for a PTFE dental floss.).

It has been well known that minor structural differences even among structurally related compounds can result in substantially different biology, expression and activities. Based on the instant disclosure one of skill in the art would not know which sequences are essential, which sequences are non-essential and what particular sequence lengths identify essential sequences for identifying a huPAP and huGM-CSF nucleic acid sequence or amino acid sequence encompassed by the claimed specificity. For example, there is insufficient guidance based on the reliance of disclosure of SEQ ID NO:1 (huPAP) or 3 (huGM-CSF) to direct a person of skill in the art to select or to predict particular sequences as essential for identifying huPAP and huGM-CSF amino acids encompassed by the claimed specificities. Mere idea of function is insufficient for written description; isolation and characterization at a minimum are required.

Scholnick et al (Trends in Biotechnology, 18(1):34-39, 2000) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based on sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to function of the structurally related protein (see in particular "Abstract" and Box 2).

Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, the replacement of a single lysine at position 118 of the acidic fibroblast growth factor by a glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (see Burgess et al, Journal of Cell Biology Vol 111 November 1990 2129-2138). In transforming growth factor alpha, replacement of aspartic acid at position 47 with asparagine, did not affect biological activity while the replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (see Lazar et al Molecular and Cellular Biology Mar 1988 Vol 8 No 3 1247-1252).

In the absence of sufficient guidance and direction to the structural and functional analysis, applicant's reliance on the activity of the huPAP and huGM-CSF polypeptides encoded by SEQ ID NOS: 1 and 3, respectively, disclosed in the specification as-filed does not appear to provide sufficient written description for the genus of amino acid sequences or nucleic acid sequences encompassed by the claimed specificities in view of the above evidence, which indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed.

For inventions in an unpredictable art, adequate written description of a genus, which embraces widely variant species cannot be achieved by disclosing only one species within the genus. In the instant case, applicant has not even disclosed a single species encompassed by the a highly variant protein moiety comprising a sequence having at least 70% sequence identity with either of SEQ ID NOS:1 (huPAP) or 3 (huGM-CSF), nor is there disclosure of the common attributes or features (i.e.,

structural domains) that are essential for activity or those which are non-essential. See, e.g., Eli Lilly. Description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces. If a representative number of adequately described species are not disclosed for a genus, the claim to that genus must be rejected as lacking adequate written description under 35 U.S.C. 112, first paragraph.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddles v.Baird, 30 USPQ2d 1481, 1483. In Fiddles v. Baird, claims directed to mammalian FGF's were

found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Therefore, only isolated amino acid sequences comprising SEQ ID NOS: 1 (huPAP) and 3 (huGM-CSF) and nucleic acids encoding SEQ ID NOS:2 (huPAP) and 4 (huGM-CSF), but not the full breadth of claims 13-15 and 17-19 meets the written description provision of 35 U.S.C. § 112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115).

11. Claims 1-15 and 17-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making and using an immunotherapeutic composition comprising APCs from a prostate cancer patient stimulated *ex vivo* by a fusion protein comprising a PAP/GM-CSF fusion protein where PAP comprises SEQ ID NO:1 and GM-GM-CSF comprises SEQ ID NO:3, does not reasonably provide enablement for making or using a immunotherapeutic composition comprising an *ex vivo* stimulated APC with just any fusion protein or a PAP/GM-CSF fusion protein where the PAP and GM-CSF are at least 70%, 80% or 90% identical to SEQ ID NOS: 1 and 3, respectively, or an *ex vivo* stimulated APC from just any kind of cancer patient stimulated with the PAP/GM-CSF fusion protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability of the art, the breadth of the claims, the quantity of experimentation which would be required in order to use the invention as claimed.

Claims 1-12 are drawn to a immunotherapeutic composition comprising an autologous APC such as a DC from a prostate cancer patient with a cancer grade of a Gleason score of ≤ 7 and being non-refractory to hormone ablation therapy, stimulated *ex vivo* with a protein conjugate of an APC binding protein and a TAA with where the N- or C-terminal moiety of the protein conjugate is the APC binding protein or the TAA with a peptide linker between the N- and C-terminal moiety. Claims 13-15 and 17-19 are drawn to a immunotherapeutic composition comprising an autologous APC from a prostate cancer patient stimulated *ex vivo* with a protein conjugate comprising an N- or C-terminal moiety having at least 70%, 80%, or 90% sequence identity with the amino acid sequence of SEQ ID NO:1 (huPAP) or 3 (huGM-CSF).

The specification teaches in general that *ex vivo* stimulated APCs are effective in activating T-cells to produce a cytotoxic cellular response against either the N-terminal moiety or the C-terminal moiety of the fusion protein, and that the level of T-cell activation is higher than that produced by the APCs when exposed to either the N-terminal moiety or the C-terminal moiety alone (p. 4, lines 14-18); treating prostate

cancer in patients with a Gleason score of ≤7 and being refractory or non-refractory to hormone ablation therapy (p. 4, lines 25-34); APCs stimulated with a protein conjugate having a C-terminal moiety or an N-terminal moiety that is at least 70%, 80%, 90%, 95%, or 98% identical to the sequence huPAP (SEQ ID NO: 1) or huGM-CSF (SEQ ID NO: 3) (p. 5, lines 7-17); obtaining and stimulating autologous APCs and DCs *ex vivo* (p. 15, lines 9-31); definitions of TAA proteins and APC binding proteins (p. 16, line 35 to p. 17, line 6); construction of PAP/GM-CSF fusion proteins fusing the PAP cDNA (SEQ ID NO: 2) to the GM-CSF CDNA (SEQ ID NO: 4) (Example 1); bioactivity of PAP/GM-CSF fusion proteins (Example 2); treatment of hormone refractory prostate cancer patients with the immunotherapeutic composition (Example 3); Figure 5 presents data demonstrating that patients receiving the immunotherapeutic composition exhibit a statistically significant enhancement in median T-cell mediated immune response as compared to patients receiving placebo (p-value = 0.0003); Figure 6 presents data demonstrating that the patient population having a Gleason score of ≤7 and receiving the composition exhibit a statistically significant enhancement in median T-cell mediated immune response as compared to a patient population having a Gleason score of 18 and receiving the composition (p-value = 0.0065); Figure 7 depicts the corresponding amino acid sequences, SEQ ID NOS: 1 and 3, for huPAP and huGM-CSF, respectively.

a. The success of DC vaccinations in treating any patient with just any cancer is unpredictable.

Claims 1-12 are not commensurate in scope with the enablement provided in the specification. The specification does not support the broad scope of the claims which

encompass autologous DC vaccines for treating just any tumor in any patient using a TAA-pulsed DC much less a protein conjugate comprising a fusion protein comprising an APC-binding protein linked by peptide linker to a TAA.

Markiewicz and Kast (Cancer Invest. 22:417-434 (2004)) discuss clinical studies using protein-pulsed DC vaccination approaches in general (p. 423, Col. 1, ¶2), and specifically mention the success in reducing serum PSA by 50% in hormone refractory cancer patients administered DCs pulsed with a GM-CSF-PAP fusion protein, and breaking of T cell immune tolerance by this composition after vaccination. Rini (Curr. Opin. Mol. Therap. 4:76-79 (2002)) discusses the clinical trial status of the therapeutic composition of APC-8015 (GM-CSF-PAP fusion protein) in the treatment of hormone-refractory prostate cancer. Despite the observed successes of the GM-CSF-PAP fusion protein for some prostate cancer treatments, Markiewicz discloses the limitations of DC vaccination in general, stating that:

> "A major concern is that DC vaccination could result in tolerance induction to the immunizing antigen. It has been reported that immature DCs can induce tolerance to antigens used for vaccinations by inducing IL-10 producing T cells...Another potential detrimental effect of DC vaccination is induction of an autoimmune response. Although no pathological autoimmune diseases have been observed in patients following immunization with tumor-associated antigen-pulsed DCs, autoimmunity is a serious possible side effect of DC immunotherapy when the antigen used for immunization is not only expressed in tumor cells, but also in normal tissue...DC vaccination seems to only be effective in early stages of tumor growth. In animal models, very advanced tumors cannot be successfully treated with DC-based immunotherapy by itself." (p. 427, Col. 2, ¶2- p. 428, Col. 1, ¶1)

Based on the unpredictability of DC vaccines in general and the lack of enablement in the specification for using the immunotherapeutic composition to treat just any patient diagnosed with just any cancer, one skilled in the art would be required to identify not only which TAA and APC-binding protein could stimulate DCs ex vivo, but to generate a recombinant protein conjugate with a suitable peptide linker which retained the biological and ex vivo DC-immunostimulatory activity for each of the separate protein moieties, in addition to testing the therapeutic effects of the composition in cancer cell lines or animal cancer models to show that the composition was specific in its immunogenicity for eliciting a T cell response. Because none of these steps are taught in the specification, undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

b. Claims 13-15 and 17-19 are not enabled for the claimed variability in the protein sequence identity for both the huPAP or huGM-CSF moieties of the protein conjugate.

Claims 13-15 and 17-19 are not commensurate in scope with the enablement provided in the specification. The specification does not support the broad scope of the claims which encompass amino acid sequences for both huPAP and huGM-C having at least 70%, 80% or 90% sequence identity with their respective amino acid sequences because the specification does not disclose the following:

The general tolerance to modification and extent of such tolerance;

The specific positions and regions of the sequence(s) which can be predictably modified and which regions are critical; and

The specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed protein in manner reasonable correlated with the scope of the claims broadly including any number of additions, deletions, substitutions or insertions. The scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 19 24 (CCPA 1970).

Without such guidance, the changes which can be made in the protein's structure and still maintain biological activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F,2d 1200, 18 USPQ 1016 (Fed. Cir. 1991) at 18 USPQ 1026 1027 and Ex parte Forman, 230 USPQ 546 (BPAI 1986).f

Further protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, see Burgess et al, (Journal of Cell Biology Vol 111 November 1990 2129-2138) and Lazar et al (Molecular and Cellular Biology Mar 1988 Vol 8 No 3 1247-1252) as discussed supra. Replacement of the histidine at position 10 of the B-chain of human insulin with aspartic acid converts the molecule into a superagonist with 5 times the activity of nature human insulin. Schwartz et al, Proc Natl Acad Sci USA Vol 84:6408-6411 (1987). Removal of the amino terminal histidine of glucagon substantially decreases the ability of the molecule to bind to its receptor and activate adenylate cyclase. Lin et al Biochemistry USA Vol 14:1559-1563 (1975). These references demonstrate that even a single amino acid substitution or what

appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of the protein.

The specification provides no direction or guidance regarding how to produce huPAP/huGM-CSF fusion proteins as broadly defined by claims 13-15 and 17-19. The specification provides no direction or guidance regarding which of any of the infinite modifications to either one or both of the huPAP and huGM-CSF moieties would still retain the ex vivo APC stimulating activity in order to formulate in the instantly claimed immunotherapeutic composition. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

Therefore, in view of the lack of guidance, lack of examples, and lack of predictability associated with regard to producing and using the myriad molecules encompassed in the scope of the claims, one skilled in the art would be forced into undue experimentation in order to practice the broadly claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 1-12, 16 and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Small et al. (J. Clin. Oncol. 18:3894-3903 (2000); hereinafter referred to as "Small").

Claims 1-12 are drawn to a immunotherapeutic composition comprising an autologous APC such as a dendritic cell from a prostate cancer patient having a moderate to well differentiated cancer grade, having a Gleason score of ≤ 7, being non-refractory to hormone ablation therapy, stimulated *ex vivo* with a protein conjugate comprising an APC binding protein and a tumor-associated antigen where the N- or C-terminal moiety of the protein conjugate is the APC binding protein or the TAA and a peptide linker is positioned between the N- and C-terminal moiety. Claims 16 and 20 are drawn to a immunotherapeutic composition comprising an autologous APC from a prostate cancer patient stimulated *ex vivo* with a protein conjugate comprising an N- or C-terminal moiety comprising an amino acid sequence of SEQ ID NO:1 (huPAP) or SEQ ID NO:3 (huGM-CSF).

The specification defines "prostate cancers having a Gleason score of ≤7, wherein a Gleason score of ≤7 indicates the presence of moderately to well-differentiated cancer cells" [0018]. The specification defines APC8015 as an "immunotherapeutic composition comprising APCs stimulated with a PAP/GM-CSF fusion protein", PA2024 (Example 3) comprising SEQ ID NOS: 1 and 3.

Small discloses a dendritic cell product, APC8015, consisting of autologous dendritic cells from patients with hormone-refractory prostate cancer loaded with a fusion protein consisting of full length PAP and full length human GM-CSF (p.3895, Col. 2, ¶ 4); autologous T cell stimulation from a patient receiving the product (Figure 3); improved disease progression as correlated with dose of product (Figures 5 and 6); "this trial establishes the groundwork for future refinements, including optimization of dosing

schedule, use in patients with less extensive disease, and possibly in combination with other therapeutic agents" (p.3902, Col. 2, ¶3).

Because the claims recite "comprising" language, APCs obtained from prostate cancer patients with "well differentiated cancer grade" are considered to encompass APCs from advanced disease in addition to "patients with less extensive disease", and thus the claims are anticipated by Small.

13. Claims 1-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Burch et al. (Clin. Cancer Research 6:2175-2182 (June 2000); hereinafter referred to as "Burch").

The interpretation of Claims 1-12, 16 and 20 is discussed supra.

Burch discloses autologous dendritic cells obtained from advanced hormone-refractory prostate cancer patients and pulsed *ex vivo* with PA2024, a recombinant protein consisting of full-length huPAP fused through its COOH terminus to the full-length NH2 terminus of GM-CSF through a Gly-Ser linker. Burch discloses that "for patients with advanced disease, standard care includes hormone ablation...[and that] initially most patients respond to this treatment, but in more than one half the disease becomes refractory to hormone therapy in <2 years. The treatment of hormone-refractory disease is less than satisfactory" (p.2175, Col. 2, ¶1). Burch discloses that the composition primes rat dendritic cells to induce anti-PAP cellular immunity (p. 2175, Col. 2, ¶3), and in their Phase I clinical trial for the composition in human prostate cancer

patients, "Four weeks after the treatment with APC8015, T cells from all evaluated patients proliferated in vitro in response to PA2024" (p. 2178, Col. 2, ¶2; Figure 3).

Because the claims recite "comprising" language, APCs obtained from prostate cancer patients with "well differentiated cancer grade" are considered to encompass APCs from advanced disease, and thus the claims are anticipated by Burch.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claims 1-12, 16 and 20 are rejected under 35 U.S.C. 103(a) as being unpatenable over Laus et al. (USPN 6,210,662, published April 3, 2001, filed June 24, 1999; hereinafter referred to as "Laus") in view of Small et al. (J. Clin. Oncol. 18:3894-3903 (December 2000); hereinafter referred to as "Small").

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The interpretation of Claims 1-12, 16 and 20 is discussed supra.

Laus discloses in general a therapeutic composition for stimulating a cellular immune response using an isolated, stimulated potent antigen presenting cell, such as an activated dendritic cell (Col. 3, lines 30-33); the APC is stimulated by exposing the cell in vitro to a polypeptide complex consisting essentially of a dendritic cell-binding protein and a polypeptide antigen where the polypeptide antigen is either a tissue-specific tumor antigen or an oncogene gene product (Col. 3, lines 39-42); the dendritic cell-binding protein of the polypeptide complex is GM-CSF, the tumor-specific antigen is prostatic acid phosphatase and between the dendritic cell-binding protein and the polypeptide antigen, is a linker peptide (Col. 3, lines 46-55; Example 1); immunostimulatory fusion proteins (Col. 4, line 27); FIG. 2 shows the amino acid sequence of the fusion protein Human Prostatic Acid Phosphatase/Human GM-CSF; formation of polypeptide complexes (Col. 7, line 53- Col. 9, line 16); in vivo therapy administering directly to an individual as a dendritic cell vaccine (Col. 4, lines 4-13; Col. 11, lines 15-19); induction of prostate cancer specific CTL by the PAP-GM-CSF protein (Example 4); amino acid residues 1-386 for SEQ ID NO: 2 of Laus are identical to SEQ ID NO:1 for huPAP (see sequence search result), amino acid residues 389-515 for SEQ ID NO:2 of Laus are identical to amino acid residues 18-144 of SEQ ID NO:3 for huGM-CSF, and the two moieties are joined by a peptide linker, Gly-Ser, at amino acid residues 387 and 388 of SEQ ID NO:2 of Laus. Laus does not teach that the prostate

cancer patient from which APCs are obtained has a moderate to well differentiated cancer grade, has a Gleason score ≤7 and is not refractory to hormone ablation therapy. Small rectifies these deficiencies in its disclosure.

See the interpretation of Small as discussed supra.

It would have been *prima facie* obvious to have produced the instantly claimed immunotherapeutic composition in view of Laus and Small.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have produced the instant claimed method in view of Laus and Small because Laus discloses the protein conjugate or fusion protein of the instantly claimed composition, and obtaining dendritic cells from autologous subjects to treat a relevant tumor bearing a tumor-associated antigen and encoded by the protein conjugate. Small discloses the using the same protein conjugate or fusion protein of Laus and the instantly claimed composition for stimulating autologous dendritic cells from advanced-stage prostate cancer patients, administering the cells into patients and observing cytotoxic T-cell specific responses. Small discloses the general need for treating prostate cancer with autologous dendritic cell immunotherapy and in patients with less extensive disease, and the more urgent need to find therapies for hormone refractory prostate cancers, thus it would have been *prima facie* obvious to have used ex vivo stimulated APCs from hormone non-refractory subjects, since Small demonstrates positive clinical results using the therapeutic composition in subjects with the highest morbidity statistics- those with well differentiated cancer grades being hormone refractory. Because of Laus' and

Small's success in stimulating prostate cancer-specific T cell immune response in vitro and in vivo, respectively, one skilled in the art at the time of the invention could have been reasonably assured of producing an immunotherapeutic composition comprising dendritic cells obtained from a patient diagnosed with a moderate to well differentiated cancer and being hormone non-refractory, in addition to being enabled for stimulating the dendritic cells ex vivo with the PAP-GM-CSF protein conjugate to produce an immunotherapeutic composition. Thus Claims 1-12, 16 and 20 were prima facie obvious in view of Laus and Small.

14. Claims 1-12, 16 and 20 are rejected under 35 U.S.C. 103(a) as being unpatenable over Fikes et al. (US20040037843, published February 26, 2004, filed December 20, 2000; hereinafter referred to as "Fikes") in view Small et al. (J. Clin. Oncol. 18:3894-3903 (December 2000); hereinafter referred to as "Small").

The interpretation of Claims 1-12, 16 and 20 is discussed supra.

Fikes discloses prostate tumor epitope-based vaccines combining selected epitopes (CTL and HTL), and modifying the composition of the epitopes for achieving, for example, enhanced immunogenicity [0014]; a list of target TAAs includes PAP [0027]; vaccines comprising peptide-pulsed antigen presenting cells, e.g., dendritic cells [0064]; expression of the fusion proteins [0186]; a bi-cistronic expression vector which allows production of both the minigene-encoded epitopes and a second protein (included to enhance or decrease immnunogenicity) including cytokines such as IL-2, IL-12, GM-CSF [0230]; administration to a prostate cancer patient who has a

malignancy associated with expression of one or more prostate-associated antigens [0252]; linked epitopes (Claims 10 and 23). Fikes does not teach that the prostate cancer patient from which APCs are obtained has a moderate to well differentiated cancer grade, has a Gleason score ≤ 7 and is not refractory to hormone ablation therapy. Small rectifies these deficiencies in its disclosure.

The interpretation of Smart is discussed supra. Smart discloses the PA2024 antigen consisting of full length human PAP and full-length human GM-CSF.

It would have been *prima facie* obvious to have produced the instantly claimed immunotherapeutic composition in view of Fikes and Small.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have produced the instant claimed immunotherapeutic composition in view of Fikes and Small because Fikes teaches that DC can be pulsed ex vivo with a cocktail of peptides (e.g., fusion proteins comprising PAP and GM-CSF), some of which stimulate CTL response to one or more antigens of interest, e.g., prostate-associated antigens such as PSA, PSM, PAP, kallikrein, and the like for administering to prostate cancer patients. Small discloses the using a PAP-GM-CSF protein conjugate or fusion protein for stimulating autologous dendritic cells from advanced-stage prostate cancer patients, administering the cells into patients and observing cytotoxic T-cell specific responses. Small discloses the general need for treating prostate cancer with autologous dendritic cell immunotherapy and in patients with less extensive disease, and the more urgent need to find therapies for hormone refractory prostate cancers, thus it would have been

prima facie obvious to have used ex vivo stimulated APCs from hormone non-refractory subjects, since Small demonstrates positive clinical results using the therapeutic composition in subjects with the highest morbidity statistics- those with well differentiated cancer grades being hormone refractory. Because of Fikes' and Small's success in stimulating prostate cancer-specific T cell immune response in vitro and in vivo, respectively, one skilled in the art at the time of the invention could have been reasonably assured of producing an immunotherapeutic composition comprising dendritic cells obtained from a patient diagnosed with a moderate to well differentiated cancer and being hormone non-refractory, in addition to being enabled for stimulating the dendritic cells ex vivo with the PAP-GM-CSF protein conjugate to produce an immunotherapeutic composition. Thus Claims 1-12, 16 and 20 were prima facie obvious in view of Fikes and Small.

Conclusion

15. No claims are allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER

Notice to Comply	Application No. 10/666,122	Applicant(s) LAUS et al.	
	Examiner Lynn Bristol	Art Unit 1643	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other:

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", **as well as an amendment specifically directing its entry into the application**.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216 or (703) 308-2923
For CRF Submission Help, call (703) 308-4212 or 308-2923
PatentIn Software Program Support
Technical Assistance.....703-287-0200
To Purchase PatentIn Software.....703-306-2600

PLEASE RETURN A COPY OF THIS NOTICE WITH YOUR REPLY

Applicant is required to provide the names of all inventors on the Sequence Listing pursuant to 37 CFR 1.823. The instantly filed Sequence Listing lists the names of Inventor Small and Inventor Rini. If Applicants intend to correct the inventorship, they will need to provide a revised Sequence Listing, a computer readable form of the Sequence Listing and a statement. This is a provisional objection to the Sequence Listing Requirements based on Applicants providing the Office with documentation that inventorship is to be corrected.